

Comparative Evaluation of Dexmedetomidine and Esmolol on Hemodynamic Responses During Laparoscopic Cholecystectomy

VINIT K. SRIVASTAVA¹, VAISHALI NAGLE², SANJAY AGRAWAL³,
DIWAKAR KUMAR⁴, AMIT VERMA⁵, SUNIL KEDIA⁶

ABSTRACT

Background: The advent of laparoscopic surgery has benefited the patient and surgeon; however creation of pneumoperitoneum for same has bearings during the perioperative period. These effects of pneumoperitoneum are associated with significant haemodynamic changes, increasing the morbidity of the patient.

Aim: The present study compared the efficacy of dexmedetomidine and esmolol on hemodynamic responses during laparoscopic cholecystectomy

Materials and Methods: A total of 90 patients aged 20-60 y, American Society of Anaesthesiologists (ASA) physical status I or II, of either sex, planned for laparoscopic cholecystectomy were included. The patients were randomly divided into three groups of 30 each. Group D received dexmedetomidine loading dose 1 mcg/kg over a period of 15 min and maintenance 0.5 mcg/kg/h throughout the pneumoperitoneum. Group E received esmolol loading dose 1 mg/kg over a period of 5 min and maintenance 0.5 mg/kg/h throughout the pneumoperitoneum. Group C received same volume of normal saline.

Measurements: Heart rate (HR), systolic blood pressure, diastolic blood pressure and mean arterial pressure (MAP) were recorded preoperative, after study drug, after induction, after intubation, after pneumoperitoneum at 15 min intervals, post pneumoperitoneum and postoperative period after 15 min. Propofol induction dose, intraoperative fentanyl requirement and sedation score were also recorded.

Results: In group D, there was no statistically significant increase in HR and blood pressure after pneumoperitoneum at any time intervals, whereas in Group E, there was a statistical significant increase in MAP after pneumoperitoneum at 15, 45, and 60 min only and HR during the whole pneumoperitoneum period. There was a significant decrease in induction dose of propofol and intraoperative fentanyl requirement in Group D and E, compared to Group C ($p < 0.0001$).

Conclusion: Dexmedetomidine is more effective than esmolol for attenuating the hemodynamic response to pneumoperitoneum in elective laparoscopic cholecystectomy. Dexmedetomidine and esmolol also reduced requirements of anaesthetic agents.

INTRODUCTION

Laparoscopic surgical procedures have various benefits to the patient in terms of decreased tissue damage, early ambulation, decreased hospital stay, reduced analgesic needs. However creation of pneumoperitoneum has its own disadvantages in terms of adverse hemodynamic cardiovascular, respiratory, stress response and acid base physiology. The increase in mean arterial pressure (MAP) and systemic vascular resistance (SVR) occurring immediately at the induction of pneumoperitoneum is suggestive of involvement of the sympathetic nervous system [1]. These hemodynamic responses are due to increased release of catecholamines, vasopressin, or both [2,3]. These complications are not serious enough in ASA I and II patients, but an exaggerated response to pneumoperitoneum has been reported in elderly and ASA III patients particularly with compromised cardiovascular system physiology.

The control and modification of these hemodynamic changes have opened a whole new chapter in the field of anesthesiology. Several modifications in technique have been tried to attenuate these responses. Various pharmacological agents like nitroglycerine [4], beta blockers [5], opioids [6], gabapentin [7], pregabalin [8], magnesium sulfate [9], clonidine [10] and dexmedetomidine [11] are used to provide hemodynamic stability during pneumoperitoneum with varying success rate.

Dexmedetomidine modulates the hemodynamic changes induced by pneumoperitoneum by inhibiting the release of catecholamines

Keywords: α_2 agonist, General anesthesia, Pneumoperitoneum

and vasopressin [12]. Esmolol, an ultra short-acting cardio-selective β_1 -receptor antagonist, has been shown to blunt hemodynamic responses to perioperative noxious stimuli [13,14]. There are few studies demonstrating the effectiveness of esmolol and dexmedetomidine individually in attenuation of hemodynamic response during laparoscopy. However, there is no study to compare the effects of esmolol and dexmedetomidine on hemodynamic response during laparoscopic cholecystectomy. Hence, the present prospective, randomized study is designed to evaluate and compare the efficacy of esmolol and dexmedetomidine on hemodynamic response during laparoscopic cholecystectomy.

MATERIALS AND METHODS

This prospective, randomized, study was conducted after approval from the institutional ethics committee and written informed consent from the patients.

A total of 102 patients, aged 20-60 y, ASA physical status I or II, of either sex, scheduled for elective laparoscopic cholecystectomy under general anesthesia were taken as subjects for the study. The exclusion criteria included the following: history of hypertension, morbid obesity, allergy to study medications, renal or hepatic insufficiency and cardiopulmonary or respiratory problems. On arrival in the operating room, five-lead surface electrocardiogram (ECG) monitoring, pulse oximetry and noninvasive blood pressure monitoring were attached (Philips IntelliVue MP 40 Monitor). In

addition, the electroencephalographic bispectral index (BIS) value was obtained using a single channel sensor (BIS Quatro™, Covidien, Mansfield, MA, USA) in a frontal temporal montage. Patients were randomized with the help of a computer-generated table of random numbers into three groups depending on the drug given.

Group D – Dexmedetomidine loading dose 1mcg/kg before induction over a period of 15 minutes and maintenance 0.5 mcg/kg/h throughout the pneumoperitoneum.

Group E – Esmolol loading dose 1 mg/kg before induction over a period of 5 minutes and maintenance 0.5 mg/kg/h throughout the pneumoperitoneum.

Group C - The same volume of normal saline was administered to the control group.

Patients will be induced 5 min after loading dose of study drug. All the drugs were prepared by an independent anesthesiologist not involved in the study, in identical syringes and infused with infusion pump (perfusor compact, B Braun).

The patients were pre-oxygenated with 100% O₂ by a face mask for 3 min. Anaesthesia was induced with midazolam 0.03 mg/kg, fentanyl 1.5 mcg/kg and propofol 1-2 mg/kg body weight followed by vecuronium 0.15 mg/kg body weight. Orotracheal intubation with Macintosh laryngoscope was done with an appropriate size cuffed endotracheal tube. Maintenance of anaesthesia was done with oxygen:nitrous oxide (O₂:N₂O; 50:50), sevoflurane, and intermittent boluses of vecuronium (0.015 mg/kg) and fentanyl (0.5 mcg/kg). Patients were closely monitored throughout the intraoperative and immediate postoperative period. Ventilation was adjusted to maintain an end-tidal carbon dioxide (ETCO₂) value between 35 and 40 mm Hg. Intra abdominal pressure was maintained to 14 mmHg throughout the laparoscopic procedure. A bispectral index of 40-60 was considered the target range of surgical anesthesia. The surgical technique used was identical in all the groups. As the pneumoperitoneum was released, drug infusion was stopped. Residual neuromuscular blockade was reversed with neostigmine (40 mcg/kg) and glycopyrrolate (10 mcg/kg).

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were recorded preoperative, after study drug administration, after induction, after intubation, after pneumoperitoneum at 15 min intervals, post pneumoperitoneum (PP) and postoperative (PO) period after 15 min. The Ramsay Sedation score was also recorded preoperative, after study drug and postoperative period.

Any hypotension (MAP <20% preoperative) was managed with a fluid bolus of normal saline 250-300 ml. If hypotension did not respond to fluid administration, then inj. mephentermine 5 mg i.v. was administered. If hypotension did not respond to 2 repeat doses of mephentermine then dopamine infusion was started to maintain the blood pressure. Any incidence of bradycardia (HR < 50/min) was treated with inj. atropine 0.6 mg i.v. Hypertension (MAP >20% preoperative) was managed with nitroglycerine infusion.

The sample size is calculated by power analysis, using a two-sample *t* test, with a two-sided type I error of 5% ($\alpha=0.05$) and power at 80.37 ($\alpha=0.19$). Therefore 25 patients in each group are needed. We enrolled 30 patients in each group to account for potential dropouts or protocol violations.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Graph pad prism 6.0 statistical software. Patient characteristic data were analysed with one-way analysis of variance (ANOVA) for continuous variables and Chi-square test for categorical variables. Intergroup comparison of heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were done with one way analysis of variance

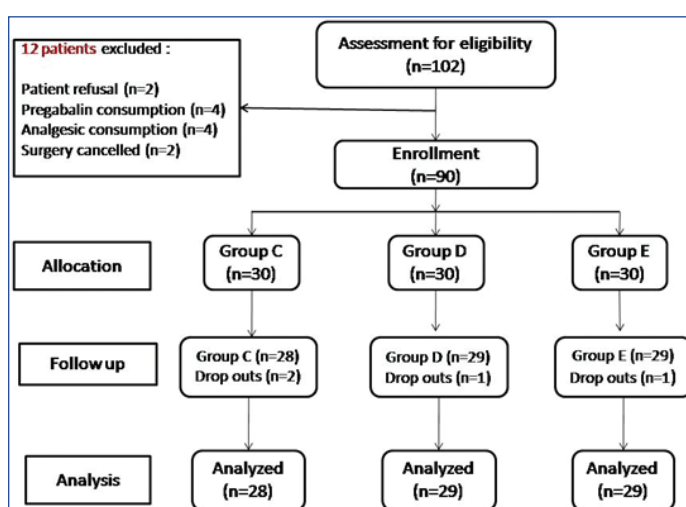
(ANOVA), followed by an unpaired *t*-test. Repeated measure analysis of variance (ANOVA) with the *post-hoc* Tukey test was used to compare means for hemodynamic variables in intragroup comparison to baseline parameters. Sedation score was analysed by the Kruskal-Wallis test. A P-value of <0.05 was considered statistically significant.

RESULTS

A total of 102 patients were assessed for eligibility, out of which ninety patients were included in the study after randomization and 86 patients (84.3%) completed the study [Table/Fig-1]. Twelve patients were excluded in this study on account of patient's refusal (two patients), pregabalin consumption (four patients), analgesic consumption (four patients) and surgery cancelled in two patients. Four patients were not included in this study on account of conversion to open cholecystectomy (one patient in Group C and Group E each), history of hypotension in Group D (one patient) which require vasopressors and one patient in Group C developed exaggerated hypertensive response during pneumoperitoneum which require administration of nitroglycerine infusion. Their data has been included in the comparison of demographic profile; however, they were not subjected to further statistical analysis.

There was no significant difference amongst the groups with regard to demographic variables ($p>0.05$) [Table/Fig-2]. Propofol induction dose and intraoperative fentanyl requirement were significantly lower in the group D (73.33 ± 11.47 mg and 41.90 ± 11.76 mcg) and Group E [89.83 ± 12.90 mg and 50.86 ± 15.01 mcg] than in the group C (105.83 ± 14.27 mg and 59.64 ± 14.78 mcg) ($p<0.0001$).

There was no significant difference in preoperative hemodynamic parameters between the groups. After administration of the study drugs, there was a significant decrease in heart rate in Group D ($p<0.05$). After induction, there was no difference in HR values between Groups C and E ($p= 0.084$). Intubation and pneumoperitoneum caused an increase in the heart rate in the Groups C and E ($p<0.05$), comparison to preoperative values, however this increase was not seen in Group D ($p>0.05$). There was no significant difference in HR values between group C and group E, during post pneumoperitoneum ($p= 0.054$) and postoperative period ($p= 0.419$) [Table/Fig-3].



[Table/Fig-1]: Study design

| Variables | Group C | Group D | Group E | p-value |
|---------------------|------------|------------|-------------|---------|
| Age (Yrs) | 42.37±8.57 | 44.96±7.54 | 47.58±10.12 | 0.073 |
| Weight (Kg) | 55.28±9.14 | 52.74±8.34 | 57.26±6.48 | 0.115 |
| Male/Female | 14/16 | 16/14 | 12/18 | 0.585 |
| Duration of surgery | 54.26±8.36 | 59.42±7.41 | 56.33±9.21 | 0.060 |

[Table/Fig-2]: Demographic profile and duration of surgery (mean ± SD)

SBP and DBP values were statistically significantly lower in the group D after induction, intubation and all time observations of pneumoperitoneum, when compared with the group C and group E ($p < 0.001$). In group C and group E, there was a statistically significant increase after intubation and during pneumoperitoneum period, but this increase was less in group E. In group D there was no statistically significant increase after intubation and at any time intervals of pneumoperitoneum [Table/Fig-4,5].

MAP-values were statistically significantly lower in the Group D comparative to Group C and Group E after intubation, all time observations of pneumoperitoneum, post pneumoperitoneum and postoperative period ($p < 0.001$). There was no significant increase in MAP in group D, compared to preoperative values at any time intervals of pneumoperitoneum, while it was a significant increase in group E and group C during pneumoperitoneum period ($p < 0.05$)

except 30th min. of pneumoperitoneum in group E ($p > 0.05$). There was no significant difference in post pneumoperitoneum MAP between the group C and E ($p = 0.363$) [Table/Fig-6].

There was no significant difference in preoperative sedation score between the groups. After study drug, sedation score was significantly higher in the Group D compared to the Group C and Group E ($p = 0.001$), while there was no significant difference in postoperative period [Table/Fig-7].

Hypotension was observed in only one patient (3.33%) receiving dexmedetomidine, which responded to administration 2 doses of mephentermine 5 mg i.v. One patient in the control group developed hypertensive response during pneumoperitoneum which was managed with nitroglycerine infusion. No side effect was observed in Group E.

| Time interval | Group C (n=28) | Group D (n=29) | Group E (n=29) | p-value | p-value | p-value |
|------------------|----------------|----------------|----------------|---------|---------|---------|
| | | | | C vs D | C vs E | D vs E |
| Preoperative | 88.79±9.96 | 87.45±9.72 | 85.10±8.76 | 0.610 | 0.143 | 0.338 |
| After Study Drug | 86.14±11.26 | 77.69±8.97* | 82.21±7.91 | <0.01 | 0.131 | <0.05 |
| After Induction | 91.14±10.05 | 80.34±7.77* | 87.03±7.44 | <0.001 | 0.084 | <0.05 |
| After Intubation | 106.18±9.07* | 88.24±9.07 | 97.38±10.17* | <0.001 | <0.01 | <0.01 |
| P 15 | 99.29±8.38* | 82.38±8.62 | 93.07±8.20* | <0.001 | <0.05 | <0.001 |
| P 30 | 98.57±8.45* | 81.45±6.54* | 90.28±7.97* | <0.001 | <0.001 | <0.001 |
| P 45 | 97.11±8.24* | 80.14±7.67* | 92.21±6.40* | <0.001 | <0.05 | <0.001 |
| P 60 | 98.04±9.07* | 79.41±7.13* | 91.34±7.06* | <0.001 | <0.01 | <0.001 |
| PP | 91.29±7.49 | 78.00±10.51* | 87.59±6.70 | <0.001 | 0.054 | <0.001 |
| PO | 90.36±7.66 | 77.38±10.74* | 88.76±7.18 | <0.001 | 0.419 | <0.001 |

[Table/Fig-3]: Changes in heart rate at various time intervals in three groups

Mean value±SD, * $p < 0.05$ within group (vs preoperative value)

P 15 – Fifteen minute, P 30 – Thirty minute, P 45 – Forty five minutes, P 60 – Sixty minute after pneumoperitoneum, PP – Post pneumoperitoneum, PO – Post operative

| Time interval value | Group C | Group D | Group E | p-value | p-value | p-value |
|---------------------|---------------|--------------|--------------|---------|---------|---------|
| | (n=28) | (n=29) | (n=29) | C vs D | C vs E | D vs E |
| Preoperative | 127.86±10.06 | 123.34±8.95 | 124.48±11.70 | 0.079 | 0.248 | 0.679 |
| After Study Drug | 124.25±9.09 | 112.28±9.42* | 118.10±9.53* | <0.001 | <0.05 | 0.022 |
| After Induction | 118.11±8.62* | 106.52±7.47* | 114.21±7.55* | <0.001 | 0.074 | <0.01 |
| After Intubation | 152.07±10.54* | 124.52± 9.32 | 138.76±9.17* | <0.001 | <0.001 | <0.001 |
| P 15 | 144.93±7.65* | 118.10±7.51 | 135.07±7.06* | <0.001 | <0.001 | <0.001 |
| P 30 | 142.36±8.29* | 120.24±6.29 | 132.93±6.57* | <0.001 | <0.001 | <0.001 |
| P 45 | 141.07±6.04* | 117.62±8.01 | 134.03±5.92* | <0.001 | <0.001 | <0.001 |
| P 60 | 143.04±6.92* | 118.03±6.68 | 135.86±7.35* | <0.001 | <0.001 | <0.001 |
| PP | 131.21±6.36 | 112.14±7.21* | 127.97±6.77 | <0.001 | 0.067 | <0.001 |
| PO | 129.07±8.15 | 114.38±9.53* | 122.24±8.11 | <0.001 | <0.05 | <0.01 |

[Table/Fig-4]: Changes in systolic blood pressure at various time intervals in three groups

Mean value±SD, * $p < 0.05$ within group (vs preoperative value)

| Time interval | Group C | Group D | Group E | p-value | p-value | p-value |
|------------------|-------------|-------------|-------------|---------|---------|---------|
| | (n=28) | (n=29) | (n=29) | C vs D | C vs E | D vs E |
| Preoperative | 79.14±10.09 | 77.62±8.08 | 79.55±7.69 | 0.531 | 0.863 | 0.355 |
| After Study Drug | 77.86±8.90 | 71.07±7.38* | 76.59±6.92 | <0.01 | 0.548 | <0.05 |
| After Induction | 74.11±7.51* | 69.31±6.07* | 71.76±8.01* | <0.05 | 0.259 | <0.001 |
| After Intubation | 95.07±8.19* | 80.07±8.17 | 89.97±9.02* | <0.001 | 0.029 | <0.001 |
| P 15 | 92.54±6.23* | 76.17±7.34 | 87.07±6.07* | <0.001 | <0.01 | <0.001 |
| P 30 | 89.36±6.63* | 74.76±8.10 | 83.97±6.83 | <0.001 | <0.05 | <0.001 |
| P 45 | 87.11±8.27* | 73.28±7.31 | 85.48±7.45* | <0.001 | 0.439 | <0.001 |
| P 60 | 87.82±6.04* | 75.34±7.82 | 82.52±8.13 | <0.001 | <0.05 | <0.01 |
| PP | 81.36±6.20 | 70.34±5.59* | 78.03±9.15 | <0.001 | 0.115 | <0.001 |
| PO | 83.21±9.18 | 68.83±6.12* | 73.38±5.85* | <0.05 | 0.060 | <0.001 |

[Table/Fig-5]: Changes in diastolic blood pressure at various time intervals in three groups

Mean value±SD, * $p < 0.05$ within group (vs preoperative value)

| Time interval | Group C | Group D | Group E | p-value | p-value | p-value |
|------------------|--------------|-------------|---------------|---------|---------|---------|
| | (n=28) | (n=29) | (n=29) | C vs D | C vs E | D vs E |
| Preoperative | 91.11±10.69 | 89.03±7.46 | 90.52±9.64 | 0.398 | 0.827 | 0.515 |
| After Study Drug | 89.21±8.92 | 80.97±6.17* | 85.28±7.94 | <0.001 | 0.083 | 0.024 |
| After Induction | 84.14±7.89* | 75.41±6.94* | 81.24±8.53* | <0.001 | 0.188 | <0.05 |
| After Intubation | 109.07±9.31* | 91.24±9.52 | 101.55±10.02* | <0.001 | <0.05 | <0.001 |
| P 15 | 104.04±8.61* | 85.21±7.95 | 98.07±7.61* | <0.001 | <0.05 | <0.001 |
| P 30 | 102.11±7.84* | 86.10±8.12 | 96.14±7.91 | <0.001 | <0.05 | <0.001 |
| P 45 | 100.96±8.45* | 84.07±8.59 | 97.10±6.60* | <0.001 | 0.059 | <0.001 |
| P 60 | 102.18±7.76* | 85.14±9.49 | 96.45±7.30* | <0.001 | <0.05 | <0.001 |
| PP | 92.29±9.36 | 81.24±7.55* | 90.03±9.19 | <0.001 | 0.363 | <0.001 |
| PO | 93.89±7.38 | 79.45±8.17* | 85.59±7.62 | <0.001 | <0.001 | <0.01 |

[Table/Fig-6]: Changes in mean arterial pressure at various time intervals in three groups

Mean value± SD, *p<0.05 within group (vs preoperative value)

| Time interval | Group C | Group D | Group E | p-value |
|------------------|-----------|-----------|-----------|---------|
| Preoperative | 2.03±0.51 | 2.38±0.62 | 2.21±0.67 | 0.085 |
| After study drug | 2.11±0.42 | 2.69±0.71 | 2.31±0.54 | 0.001 |
| Postoperative | 2.35±0.73 | 2.72±0.65 | 2.45±0.63 | 0.073 |

[Table/Fig-7]: Sedation Score at various time intervals in three groups

DISCUSSION

Our study confirms that dexmedetomidine and esmolol were successfully used to control hemodynamic changes during pneumoperitoneum in laparoscopic cholecystectomy; however dexmedetomidine is more effective than esmolol to attenuate these changes.

Laparoscopic cholecystectomy is considered a minimally invasive procedure. Pneumoperitoneum using CO₂ for laparoscopic surgery causes a rapid and immediate increase in plasma catecholamines and vasopressin, [2,3] possibly due to an increase in intraperitoneal pressure and stimulation of the peritoneum by CO₂. The increase in these stress hormones induces a cardiovascular response characterized by abrupt elevations of arterial pressure, SVR and HR [1]. The increase in these hemodynamic values significantly increases the incidence of myocardial ischemia, infarction and other complications [15]. Our study used comparison of dexmedetomidine and esmolol because both of these drugs are short acting, reduce catecholamines release and no postoperative complication.

Dexmedetomidine, a highly selective α₂ receptor agonist, provides excellent sedation and analgesia with minimal respiratory depression [16]. Esmolol, an ultra short-acting cardio-selective β₁-receptor antagonist having little sedative effect, but no analgesic activity [17]. The pharmacologic profiles and anaesthetic sparing effects of dexmedetomidine and esmolol suggested that these drugs could be a suitable anaesthetic adjuvant for attenuating acute intraoperative hemodynamic stress responses in laparoscopic cholecystectomy without interfering with the recovery process.

Previous studies report that dexmedetomidine infusion rates ranging from 0.2 to 10 mcg/kg/hr have been used. The studies with higher dose had more incidences of hypotension and bradycardia [18]. Most study used dexmedetomidine loading dose 1 mcg/kg over 10-15 minutes followed by continuous infusion 0.2 to 0.5 mcg/kg/hr for maintenance and concluded that dexmedetomidine attenuates the increase in heart rate and blood pressure by altering the stress-induced sympathoadrenal response [19,20]. In this study, we also used dexmedetomidine loading dose 1 mcg/kg over 15 minutes, followed by maintenance dose 0.5 mcg/kg/hr, which is similar to the dose used in above mentioned studies.

β-Adrenergic receptor antagonists have also been used by various authors during surgery with the intention to attenuate the stress

response and decrease unwanted perioperative hemodynamic changes. Koivusalo et al., [5] suggested that an effect of esmolol on hemodynamic response to CO₂ pneumoperitoneum is mediated by blockade of peripheral β-adrenergic receptors. In addition to this it decreased the intraoperative fentanyl requirement and also protected against renal vasoconstriction. Ozturk et al., [21] also confirmed that esmolol had an opioid sparing effect during the intraoperative and immediate postoperative period in laparoscopic cholecystectomy. Collard et al., [22] reported that intraoperative esmolol infusion facilitates earlier discharge because of decrease opioid requirement. In our study also dexmedetomidine and esmolol group had significant reduction in induction dose of propofol and intraoperative fentanyl requirement compared to control group [11,13,23,24].

Priya et al., [25] noted that single dose of dexmedetomidine and esmolol were effective in controlling rise of pulse and blood pressure during extubation phase and dexmedetomidine is more effective than esmolol because of its additional analgesic and sedative actions. We also found same results in pneumoperitoneum period with these two drugs, but contrast to this study we used loading dose and continuous infusion during whole pneumoperitoneum period. Shams, et al., [26] also used the same dose of dexmedetomidine and esmolol followed by continuous infusion for induced hypotension in FESS and found that dexmedetomidine is more effective than esmolol with the added advantages of sedative and anaesthetic sparing effect.

There are some limitations to our study: (1) the no of patients is too small for broad generalizations (2) plasma catecholamines and antidiuretic hormone levels were not assessed by us to know the degree of suppression of neurohumoral pathway (3) we did not measure the postoperative fentanyl requirement and extubation criteria.

CONCLUSION

We emphasize the use of dexmedetomidine and esmolol for attenuation of hemodynamic response to pneumoperitoneum in laparoscopic cholecystectomy. Dexmedetomidine is more effective than esmolol in preventing such hemodynamic responses in laparoscopic surgery. In addition, dexmedetomidine and esmolol also reduce the induction dose of propofol and intraoperative fentanyl requirement.

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PARTICULARS OF CONTRIBUTORS:

1. Consultant Anaesthesiologist, Department of Anaesthesiology, Apollo Hospitals Bilaspur, Chhattisgarh, India.
2. Postgraduate Trainee, Department of Anaesthesiology, Apollo Hospitals Bilaspur, Chhattisgarh, India.
3. Professor, Department of Anesthesiology, Himalayan Institute of Medical Sciences, Dehradun, India.
4. Senior Consultant, Department of Anaesthesiology, Apollo Hospitals Bilaspur, Chhattisgarh, India.
5. Senior Consultant, Department of Surgery, Apollo Hospitals Bilaspur, Chhattisgarh, India.
6. Senior Consultant, Department of Surgery, Apollo Hospitals Bilaspur, Chhattisgarh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Vinit K. Srivastava,
Consultant Anaesthesiologist, Department of Anaesthesiology, Apollo Hospitals Bilaspur, Chhattisgarh-495006, India.
E-mail: drvinit75@gmail.com

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